Inhibitory effects of ginsenoside-Rh2 epimers on Organic Anion Transporting Polypeptide (OATP) 1B3-mediated uptake

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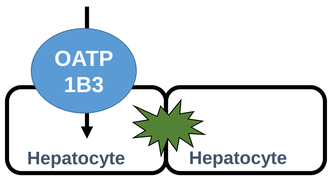
Abstract

Organic anion transporting polypeptide (OATP) 1B3 plays an essential role in the hepatic uptake of many drugs and the assessment of OATP1B3-mediated drug-drug interactions is recently emphasized. The main active components of ginseng are ginsenosides, a diverse group of triterpenoid saponins that exert a variety of pharmacological activities including anti-inflammatory, anti-cancer, anti-diabetic, and cardioprotective effects. Of these, ginsenoside Rh2 is mainly recognized as an anti-cancer compound, and contains the two epimeric forms, 20(*R*)-Rh2 and 20(*S*)-Rh2. It was reported that the stereochemistry of the C-20 hydroxyl group [i.e., 20(*R*)-Rh2 and 20(*S*)-Rh2] not only plays a role in the pharmacodynamics of ginsenosides but also in their pharmacokinetic properties. The aim of this study was to evaluate the human organic anion transporting polypeptide 1B3 (OATP1B3)-mediated drug-drug interaction potential of ginsenoside Rh2 (Rh2) epimers, 20(*R*)-Rh2 and 20(*S*)-Rh2, using human embryonic kidney 293 (HEK293) cells overexpressing OATP1B3 (HEK293-OATP1B3). The inhibition of estradiol 17β-D-glucuronide transport by ginsenoside Rh2 epimers were assessed in HEK293-OATP1B3. Our results showed that both 20(*R*)-Rh2 and 20(*S*)-Rh2 exhibited different potencies of stereoselective inhibition on the OATP1B3 uptake. 20(*S*)-Rh2 exerted marked inhibition with and IC_{50} value of 17.1 ± 7.10 μM, whereas their (*R*)-isomer did not inhibit OATP1B3 uptake activity.

Introduction

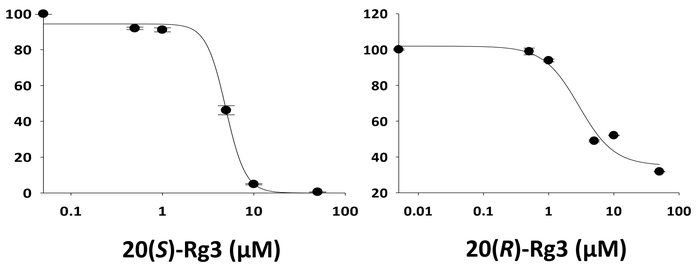
1. OATP1B3

- A product of gene SLCO1B3 and one of the best-characterized human OATPs.
- Specifically expressed on the sinusoidal membrane of human hepatocytes and plays an important role in hepatic drug uptake subsequently elimination.
- Modulation of OATP1B3 may alter the pharmacokinetics of OATP1B3 substrate drugs causing potential drug-drug interactions (DDIs).



2. Ginsenoside-Rh2

- Ginsenosides are the main bioactive components of *Panax ginseng* C.A. Meyer.
- The ginsenosides have a chiral carbon atom in position 20 and consequently exist in *R*- and *S*- configuration (20(*R*)-, 20(*S*)-).



- In previous study, 20(*S*)-Rg3 and 20(R)-Rg3 selectively inhibited OATP 1B1 and 20(S) –Rg3 presented more potent inhibitory effect than 20(*R*)-Rg3.

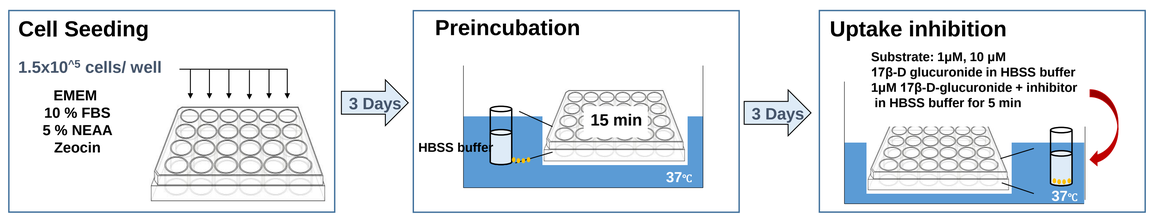
- OATP1B3-mediated DDI potential of ginsenosides has not yet been fully characterized
- The aim of the study was to evaluate the human OATP1B3-mediated DDI potential of ginsenoside Rh2 (Rh2) epimers, 20(*R*)-Rh2 and 20(*S*)-Rh2, using human embryonic kidney 293 (HEK293) cells overexpressing OATP1B3 (HEK293-OATP1B3).

Methods

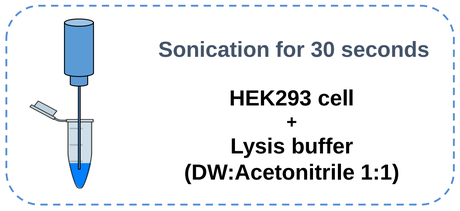
1. HEK293 cells overexpressing OATP1B3

- HEK293 cells overexpressing OATP1B3 were kindly provided by Prof. Dr. Wooin Lee (Seoul National University, Seoul, Korea).

2. OATP1B3-mediated uptake and inhibition assays



3. Sample preparation



4. Data analysis

- Rate of uptake of substrate $= \frac{\text{Substrate concentration}}{\text{Time of incubation} \times \text{protein content per well}}$
- OATP1B3 activity (%) $= \frac{\text{Rate of uptake of substrate}_{\text{Inhibitor}}}{\text{Rate of uptake of substrate}_{\text{No inhibitor}}} \times 100$
- IC_{50} was calculated by Hill equation using Sigma Plot®

Results

Fig 1. Concentration-dependent OATP1B1-mediated uptake of 1 μM estradiol 17 β glucuronide inhibition using HEK293-OATP1B3 cells.

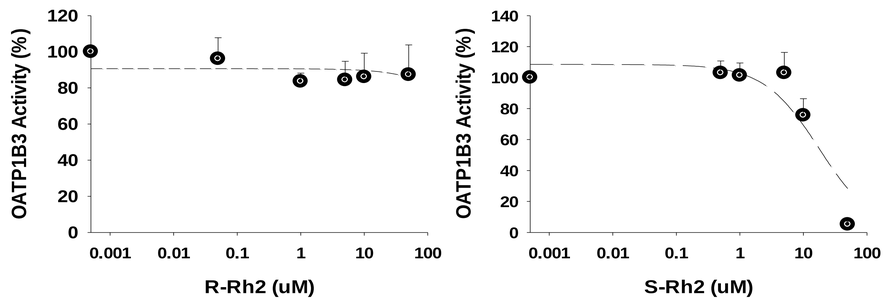
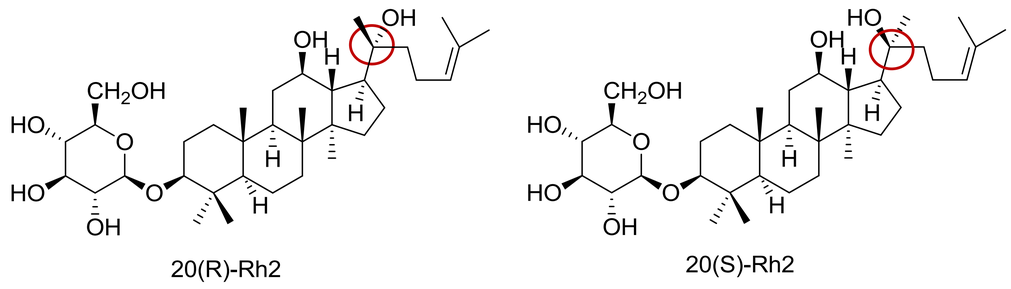


Table 1. IC_{50} of selected inhibitors towards OATP1B3

Inhibitors	IC_{50}(μM)
20(*S*)-Rh2	17.1 ± 7.10
20(*R*)-Rh2	Not inhibited

- 20(*S*)-Rh2 exerted marked inhibition with and IC_{50} value of 17.1 ± 7.10 μM, whereas their (*R*)-isomer did not inhibit OATP1B3 uptake activity.

Conclusion



- **20(*S*)-Rh2 presents more potent inhibitory effect in HEK293 cells overexpressing OATP1B3. However 20(*R*)-Rh2 has no inhibitory effect on OATP1B3.**
- **These results indicate that the stereochemistry of the C-20 hydroxyl group of Rh2 plays a role in the OATP1B3 transport.**
- **There may be a potential for DDIs between the ginsenosides and OATP1B3 substrates when concomitantly administered.**